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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,652	09/24/2001	Claudio De Simone	2818-58	5995

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/960,652	De Simone
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 7, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *25-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of claims

New claims 25-34 are pending and under examination in the instant office action. Original claims 1-24 were canceled by applicant. [Paper No. 4 filed 1/07/2003].

Election/Restriction

Applicant's election without traverse of the Group II invention, (original claims 15-24 or new claims 25-34), drawn a method of treatments with a pharmaceutical composition comprising alkaline sphingomyelinase derived from lactic bacteria, is acknowledged.

Specification

The disclosure is objected to because of the following informalities:

The contents of specification are missing identification of specification sections including section "Brief Description of the Several Views of the Drawing(s)" with a reference to and brief description of the drawing(s) before the detailed description of the invention (pages 10-13).

Appropriate correction is required.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-Reference to Related Applications.
© Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).
(e) Background of the Invention.
1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

Claim Objections

Claim 34 is objected to because of the following informalities: The Latin name of microorganisms belonging to the group o f bifidobacteria which are intended in the claimed invention should be italicized. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 25-34 are rejected under 35 U.S.C. 112, *second paragraph*, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The presently claimed invention is indefinite and incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is a link between "alkaline sphingomyelinase" enzymatic preparation (claim 25) and "live, lyophilized or sonicated bacteria" (claim 32) in the composition in the method for administration. It is uncertain what composition is administered in the claimed method. Does the claimed composition comprise an enzyme preparation derived from bacteria which is free from

bacterial cells? Does the claimed composition comprise a crude preparation of "live, lyophilized or sonicated bacteria" (claims 29 and 32)?

The claimed method is interpreted in the light of applicant's definitions in the "as-filed" specification wherein the "lactic bacteria are used in the composition as live, lyophilized or sonicated bacteria" (specification page 6, lines 20-22) in the presently elected method drawn to administration of this composition.

The claimed method is also appears to be indefinite and incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element appears to be a component which would make a composition comprising enzymatic preparation such as "live, lyophilized or sonicated bacteria" to be an "alkaline" form of sphingomyelinase enzyme. It is uncertain whether the use of a particular strain (claim 31) or a combination of particular species (claims 30 and 34) which are capable to produce only the alkaline form of sphingomyelinase, for example, are intended in the presently claimed method for administration. It is uncertain whether some unidentified component is used in the method of administering the composition in order to deactivate other forms of sphingomyelinase including acid and/or neutral sphingomyelinase.

Claim 25 is indefinite with regard to "effective" amount of alkaline sphingomyelinase in a composition in a method for administration. It is uncertain what is the difference between "prophylactic" amount and "therapeutically effective" amount for prevention and/or treatment of a large variety of different diseases, disorders and processes as claimed. The broad list of

disorders intended to be treated does not appear to benefit the claimed method because it comprises such a variety of disorders including gastro-intestinal, immune system, neonatal growth and nervous system that a reasonable determination of "prophylactic or therapeutically effective amount" is impaired in order to set forth the metes and bounds of the patent protection desired. It is also uncertain as claimed whether the phrase a "prophylactic" amount or a prophylactically "effective" amount is intended for the composition in the method of administering for prevention of various disorders.

Claim 26 is indefinite because it is uncertain as claimed what element makes the claimed composition to be a pediatric dietary supplement in the he method of administration. Is it a component in the composition to be administered or a patient under treatment? The protocol of administration is uncertain as claimed and as disclosed.

Claim 28 is indefinite because it is unclear what is "umanized" milk.

Claim 29 has an improper Markush group because it is not particularly clear what is included or what is excluded by the claim language. The members of the claimed groups are at least redundant since the lactic bacteria are Gram-positive bacteria or the lactic bacteria belong to the group of Gram-positive bacteria. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Further, the broad language such as "Gram-positive" and "Gram-negative" bacteria does not

appear to benefit the presently claimed method because all bacteria as claimed clearly include administration of pathogenic bacteria as "live" preparations (claim 32).

Claims 31-34 are rendered infinite by the phrases such as bacteria or strain "are/is used" wherein it is uncertain as claimed what is encompassed by these phrases in the claimed method for administration. Are bacteria used for administration? Are bacteria used for making an enzyme? The protocol of administration is uncertain as claimed and as disclosed.

Claim 34 is indefinite and appears to extend rather than to further limit the claimed invention. For example: claim 34 recites the broad limitation such as "Bifidobacteria" which encompasses all bacteria belonging to the group of bifidobacteria, however the method of claim 29 is drawn to particular bacterial species belonging to the genus of *Bifidobacterium* in the method for administration which is the narrower statement of the range/limitation. Moreover, in the lack of definitions what is the meaning of terminology such as "Bifidobacteria", it is uncertain what lactic bacteria would be included or excluded from the claimed group.

Deposit

Claim 31 is rejected under 35 U.S.C. 112, *first paragraph,* as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 31 requires one of ordinary skill in the art to have access to a specific microorganism such as *Lactobacillus brevis* CD2 accession No. DSM 11988. Because the microorganism is essential to the claimed invention, it must be obtainable by a repeatable method

set forth in the specification or otherwise be readily available to the public. If the microorganism is not so obtainable or available, the requirements of 35 USC 112 may be satisfied by deposit of the microorganism. The specification does not disclose a repeatable process to obtain the microorganism and it is not clear from the specification or record that the microorganism is readily available to the public.

The objection and accompanying rejection may be overcome by establishing that each microorganism identified is readily available to the public and will continue to be so for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is long er, or by an acceptable deposit as set forth herein. See 37 CFR 1.801-1.809.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or a statement by an attorney of record over his/her signature and registration number, stating that the deposit has been made under the Budapest Treaty and that all restrictions imposed by the depositor on availability to the public of the deposited material will be irrevocably removed upon issuance of the patent would satisfy the deposit requirement. See 37 CFR 1.808.

Because DSM (Deutsche Sammlung von Mikroorganismen, Germany) has acquired the status of an International Depository in accordance to the Budapest Treaty, a declaration stating that all restrictions will be irrevocably removed upon issuance of the patent will overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-30 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,716,615 [A] as evidenced by US 5,912,152 and Sugimoto [U].

Claims are directed to a method for preventing and treating various disorders including gastro-intestinal, hypocholesterolaemia and/or immune system disorders wherein the method comprises orally administering to a subject a composition comprising an effective amount of an enzymatic preparation of alkaline sphingomyelinase in a form of live or lyophilized bacteria including lactic bacteria. Some claims are further drawn to the use of effective amounts such as 10^2 - 10^{13} CFU of lactic bacteria per gram of the composition in the method of administration. Some claims are further drawn to the use of particular species of lactic bacteria such as *Steptococcus thermophilus*, *Lactobacillus acidophilus* and representatives of the genus *Bifidobacterium* in the composition in the method of administration. Some claims are further drawn to incorporation of milk product in the composition in the method of administration.

US 5,716,615 [A] discloses a method for preventing and treating various disorders including gastro-intestinal, hypocholesterolaemia and/or immune system disorders (col. 2, lines 17-20) wherein the method comprises orally administering to a subject (col. 3, line 42 or

examples) a composition comprising an effective amount of a bacterial preparation in a form of live or lyophilized bacteria including lactic bacteria such as *Steptococcus thermophilus*, *Lactobacillus acidophilus* and representatives of the genus *Bifidobacterium* (col. 3, lines 3-12 or col. 5, lines 1-11). The effective amount is ranging between 10^9 - 10^{13} CFU of lactic bacteria per gram of the composition in the method of administration (col. 5, lines 1-11 or col. 2, line 50). The cited patent teaches incorporation of milk products such as skim milk (col. 9, line 22 or col. 10, line 6) in the composition in the method of administration.

The cited patent US 5,716,615 [A] is considered to anticipate the claimed invention because the method of the cited patent comprises one identical active step of oral administration of identical bacterial composition in a form of live lyophilized lactic bacteria of identical species in the identical amount effective with respect to identical disorders as required by the presently claimed method. The enzymes of bacterial origins including alkaline sphingomyelinase are an inherent component in the composition such as a whole or crude preparation of live or lyophilized bacteria as evidenced by US 5,912,152 and Sugimoto [U]. It is known that sphingomyelinase or phospholipase are produced by bacteria (see US 5,912,152 at col. 2, lines 5-061) and that sphingomyelinase or phospholipase enzymatic preparations derived from lactic bacteria have enzymatic activity at alkaline pH (see Sugimoto [U] at abstract or table I). The present invention as claimed and as disclosed does not require administration of a pure enzyme preparation. Therefore, the cited patent US 5,716,615 [A] is considered to anticipate the claimed invention within the meaning of the present application and claims.

Claims 25, 29, 30 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/22082 [IDS-1].

Claims are directed to a method for preventing and treating various disorders including immune system disorders wherein the method comprises administering to a subject a composition comprising an effective amount of an enzymatic preparation of alkaline sphingomyelinase in a form of live, lyophilized or sonicated bacteria including lactic bacteria. Some claims are further drawn to the use of effective amounts such as 10^2 - 10^{13} CFU of lactic bacteria per gram of the composition in the method of administration. Some claims are further drawn to the use of particular species of lactic bacteria such as *Steptococcus thermophilus*, *Lactobacillus acidophilus* and representatives of the genus *Bifidobacterium* in the composition in the method of administration.

WO 98/22082 [IDS-1] discloses a method for preventing and treating various disorders including immune system disorders or eczema, dermatitis, psoriasis (page 3, lines 1-3) wherein the method comprises administering to a subject a composition comprising an effective amount of an enzymatic preparation of sphingomyelinase in a form of live, lyophilized or sonicated bacteria including lactic bacteria (page 4, line 1 and par. 2). The effective amount is 10^2 - 10^{15} CFU of lactic bacteria per gram of the composition in the method of administration. The cited patent teaches the use of particular species of lactic bacteria including *Steptococcus thermophilus*, *Lactobacillus acidophilus*, the representatives of the genus *Bifidobacterium* and *Lactobacillus brevis* (page 4, par. 1) in the composition in the method of administration.

The cited patent WO 98/22082 [IDS-1] is considered to anticipate the claimed invention because the method of the cited patent comprises one identical active step of administration of identical bacterial preparation in a form of live, lyophilized or sonicated lactic bacteria of identical species in the identical amount effective as required by the presently claimed method. The enzymes derived from bacteria including alkaline sphingomyelinase are an inherent component in the composition such as a whole or crude preparation of live, lyophilized or sonicated bacteria. Although the cited patent WO 98/22082 [IDS-1] is silent with regard to the alkaline sphingomyelinase derived from lactic bacteria, however only the acid sphingomyelinase appears to be excluded in the preparation of sonicated lactic bacteria. The present invention as claimed and as disclosed is uncertain with regard to what element makes the claimed composition, which is "live, lyophilized or sonicated lactic bacteria" to be an "alkaline" sphingomyelinase preparation. The presently claimed method dos not exclude the use of other than acid sphingomyelinase, including alkaline and/or neutral, by the virtue of the open language "comprising". Moreover, the present invention as claimed and as disclosed does not require administration of a pure enzyme preparation. Thus, there is a reasonable believe that the effects of the method of the cited WO 98/22082 [IDS-1] would be the same as the effects of the presently claimed method as results/effects of practicing identical protocol of treatment. Therefore, the cited patent WO 98/22082 [IDS-1] is considered to anticipate the claimed invention within the meaning of the present application and claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,716,615 [A] as evidenced by US 5,912,152 and Sugimoto [U] taken with WO 98/22082 [IDS-1] and Sjokvist et al. [IDS-4].

Claims are directed to a method for preventing and treating various disorders including gastro-intestinal, hypocholesterolaemia and/or immune system disorders wherein the method comprises orally administering to a subject a composition comprising an effective amount of an enzymatic preparation of alkaline sphingomyelinase in a form of live or lyophilized bacteria including lactic bacteria. Some claims are further drawn to the use of effective amounts such as 10^2 - 10^{13} CFU of lactic bacteria per gram of the composition in the method of administration. Some claims are further drawn to the use of particular species of lactic bacteria such as *Steptococcus thermophilus*, *Lactobacillus acidophilus* and representatives of the genus *Bifidobacterium* in the composition in the method of administration. Some claims are further drawn to incorporation of milk product in the composition in the method of administration. Some claims are further drawn to the use of a particular strain *Lactobacillus brevis* CD2 accession No. DSM 11988 in the composition in the method of administration.

The cited patents US 5,716,615 [A] and WO 98/22082 [IDS-1] are relied upon as explained above for the disclosure of methods for preventing and treating various disorders by administering a composition comprising an enzymatic preparation with alkaline sphingomyelinase in a form of live, lyophilized and/or sonicated lactic bacteria. The cited patent US 5,716,615 [A] teaches enteral or oral administration of preparations derived from lactic bacteria. The cited patent WO 98/22082 [IDS-1] teaches topical administration of preparations derived from lactic bacteria. Although the cited patent WO 98/22082 [IDS-1] is silent with regard to treatments of gastro-intestinal disorders, it teaches that sphingomyelinase preparations play a critical role in maintaining health of epidermal cells and mucosa (page 2, par. 1, line 8; page 3, par. 4, last line), thus, it suggests the critical role and applications of the same sphingomyelinase enzymatic preparations for all anatomic sites which have mucosa and/or epidermal cells including gastro-intestinal tract. Both cited patents US 5,716,615 [A] and WO 98/22082 [IDS-1] teaches the use of the same effective amounts of lactic bacteria in the method of administration. Both cited patents US 5,716,615 [A] and WO 98/22082 [IDS-1] teaches the use of the same species lactic bacteria including *Steptococcus thermophilus*, *Lactobacillus acidophilus* and representatives of the genus *Bifidobacterium* in the composition in the method of administration for treating a large variety of disorders.

But the cited patents US 5,716,615 [A] and WO 98/22082 [IDS-1] are missing the disclosure about the use of a particular strain *Lactobacillus brevis* CD2 accession No. DSM 11988 in the composition in the method of administration. However, both patents teach that a

large variety of lactic bacteria are suitable for treating the same disorders as intended by the presently claimed invention. Moreover, WO 98/22082 [IDS-1] teaches application of the same species of *Lactobacillus brevis* (page 4, last line) in the composition for the same purpose as encompassed by the claimed method.

In addition, the cited patent US 5,912,152 and the reference by Sugimoto [U] are relied upon as explained above to demonstrate that enzymes of bacterial origins including alkaline sphingomyelinase are an inherent component in the composition such as a whole or crude preparation of live, lyophilized or sonicated bacteria including lactic bacteria.

Further, the reference by Sjokvist et al. [IDS-4] is relied upon to demonstrate that development of gastro-intestinal disorders is connected to a reduction in amounts and/or activity of alkaline sphingomyelinase in a gastro-intestinal tract.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice administration of crude enzymatic preparation in a form of live, lyophilized or sonicated lactic bacteria including alkaline sphingomyelinase with a reasonable expectation of success in treating various disorders including gastro-intestinal and/or immune system disorders as taught by US 5,716,615 [A] and WO 98/22082 [IDS-1]. One of skill in the art would have been motivated to administer enzymatic preparations with alkaline sphingomyelinase for at least prevention, if not a treatment, of gastro-intestinal disorders since the reduction in amounts and/or activity of alkaline sphingomyelinase in a gastro-intestinal tract is connected to a development of gastro-intestinal disorders as taught Sjokvist et al. [IDS-4]. One

of skill in the art would have been motivated to administer a composition with lactic bacteria because the lactic bacteria are known to provide a spectrum of health benefits to patents under treatment including prevention and treatment of gastro-intestinal, hypocholesterolaemia and/or immune system disorders. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. With respect to claim 31 it is uncertain as claimed and as disclosed what are the differences between the strain *Lactobacillus brevis* CD2 accession No. DSM 11988 and the other representatives of the lactic bacteria group including representatives of the species of *Lactobacillus brevis* in the claimed method for administration intended to treat the disorders as claimed. It is uncertain whether a live, lyophilized or sonicated preparation of the strain DSM 11988 would not comprise other bacterial enzymes than sphingomyelinase in the claimed method for administration intended to treat the disorders as claimed.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

Art Unit 1651

March 14, 2003.

VERA AFREMOVA

PATENT EXAMINER